REMARKS

Initially, Applicants direct the Office's attention to the Utility Transmittal cover sheet filed with the present application on November 9, 2001. According to the Transmittal, claims 1-23, 36-48, and 50 were cancelled. Since the first and second Restriction Requirements did not take into consideration the already cancelled claims, it is unclear which claims are currently pending, and which are cancelled. Accordingly, in the present amendment, Applicants have cancelled claims 1-50 and introduced new claims 51-71. New claims 51-60 are analogous to original claims 1-8 and 10-11, which were elected in response to the Restriction Requirement of December 30, 2004.

Applicants also note that in the present Office Action claims 1-8 and 10 are listed as pending. However, the elected invention (Group I) includes claim 11. Applicants assume that the omission of claim 11 from the list of pending claims was an error.

As indicated above, new claims 51-60 are analogous to elected claims 1-8 and 10-11. New claims 61-67 are directed to a method for screening compounds that function as inverse agonists at both an $\alpha_1\beta_2\gamma_2$ and an $\alpha_5\beta_3\gamma_2$ $GABA_A$ subtype receptor. Support for new claims 61-67 can be found in the specification at page 23, middle, to page 24, first paragraph. New claims 68-71 are directed to a method for screening compounds with agonist

activity at an $\alpha_1\beta_2\gamma_2$ receptor subtype and inverse agonist activity at an $\alpha_5\beta_3\gamma_2$ receptor subtype. Support for new claims 68-71 can be found, for example, in Table 1 and accompanying text. With these amendments, claims 51-71 are pending.

In the specification at page 2, Applicants have inserted the correct priority information for this application. The priority paragraph has also been amended to correct a typographical error.

The claim rejections are addressed below.

Rejections Under 35 U.S.C. § 103(a)

Claims 1-8 and 10 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent 6,426,343 ("Dawson I") and, separately, as being unpatentable over WO 96/25948 ("Dawson II"). Applicants respectfully disagree with the rejection.

It is respectfully submitted that the Office has misunderstood at least a portion of the invention. At page 3 of the Office Action, the Office states:

> The invention of the instant claims is predicated on the idea that selective inverse agonism of GABA alpha 5 receptors, while minimizing activity of receptors having alpha 2 and 3 receptor subtypes, will produce cognitive enhancing effects while minimizing pro-convulsive effects, see page 9.

This statement is not accurate. Page 9 of the specification states that selected compounds of the assay exhibit inverse agonism at $\alpha_1\beta_2\gamma_2$ or $\alpha_5\beta_3\gamma_2$ and produce agonist activity at

receptors containing the α_2 or α_3 subunit. These selection parameters are reflected in claims 1-8 and 10-11 (now claims 51-60). Indeed, all of the pending claims require the selected compounds to exhibit some agonist activity at receptors comprising an α_2 or α_3 subunit.

Neither Dawson I nor Dawson II[1] discloses an assay in which the selected compound exhibits agonist activity at receptors comprising an α_2 or α_3 subunit. In fact, each reference explicitly teaches away from this requirement. The references describe the use of α5 selective compounds as cognitive enhancers. See e.g., Dawson I, col. 1, lines 5-7 and lines 42-43. In general, such compounds are said to bind as inverse agonists at α5 receptors, and have no significant agonist or inverse agonist binding at α1 receptors and (preferably) at α2 and α3 receptors as well. See for example, Dawson I, col. 1, lines 58-67. The Dawson references therefore clearly teach away from screens in which compounds having any inverse agonist activity or agonist activity at α1, α2 or α3 are selected. All of the presently pending claims include a step in which selected compounds have agonist activity at α2 or α3. Thus the references clearly teach away from the claimed invention.

[1] Dawson I appears to be the U.S. national phase of Dawson II, a PCT application. For simplicity, Applicants have cited to Dawson I in the present response and occasionally refer to the Dawson reference in the singular. It is understood, however, that all of Applicants comments herein apply to both Dawson references.

Another significant distinction between the presently claimed invention and the Dawson references is Dawson's reliance on binding affinity for identifying compounds. As described in the Applicants' specification, EC_{50} values do not necessarily correlate with binding affinities or efficacies (page 8, lines 1-15), and the claimed methods may be performed without measuring binding affinities (page 7, lines 12-14). In contrast, Dawson identifies its compounds as having high binding affinities K_i (e.g., Dawson I, col. 2, lines 60-65) and uses screening methods based on binding affinity (Dawson I, col. 5, line 65 to col. 6, line 15). Binding affinity was the basis for conventional screening methods for receptor-selective compounds. See Paul J. Whiting, "The $GABA_A$ receptor gene family: New opportunities for drug development," 6 Current Opinion in Drug Discovery & Development, 648-57, 652 (2003) (copy provided with this paper) ("The traditional approach to develop compounds that are selective for, for example, a receptor subtype, is to aim for binding affinity or selectivity, which can be achieved through the use of conventional radioligand binding assays.") The skilled artisan reading Dawson would be taught that binding affinity is the important parameter, and conduct conventional screening assays based on binding affinity, not on efficacy and EC_{50} values.

For at least the foregoing reasons, it is respectfully submitted that the claimed invention would not have been obvious to a person of ordinary skill in the art. Reconsideration and withdrawal of the § 103 rejections based on the Dawson references is therefore respectfully requested.

New Claims 61-71 are Allowable

New claims 61-67 are directed to screening methods in which compounds are identified, in part, based on inverse agonist activity at $\alpha_1\beta_2\gamma_2$ and $\alpha_5\beta_3\gamma_2$ $GABA_A$ subtype receptors. Thus, in addition to being allowable for the reasons discussed above for claims 51-60 (e.g., the prior art teaches away from the claimed step of screening based on activity at α2 or α3), claims 61-67 are also allowable because the cited prior art does not teach identifying compounds based on both α1 and α5 activity.

New claims 68-71 are directed to screening methods in which compounds are identified, in part, based on inverse agonist activity at $\alpha_5\beta_3\gamma_2$ and agonist activity at $\alpha_1\beta_2\gamma_2$. Again, in addition to being allowable for the same reasons discussed above, claims 68-71 are also allowable because the cited prior art does not teach identifying compounds based on agonist activity at α1 and inverse agonist activity at α5.

Allowance of all the pending claims and passage of the case to issue are respectfully solicited. Should the Examiner

believe that a discussion of this matter would be helpful, the Examiner is invited to telephone the undersigned at (312) 913-0001.

Respectfully submitted,

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DATED: August 4, 2005

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